

## AMENDMENTS

### Amendments to the Specification:

Please add the following new paragraph after the title on page 1:

This application is a divisional application of U.S. Patent Application Serial No. 09/564,351, which claims the benefit under 35 U.S.C. §120 and 365(c) of international PCT Application PCT/EP98/06755, filed October 23, 1998, designating the United States, which claims the benefit of prior European application EP 97118457.7, filed October 23, 1997.

Please add the following new paragraph at page 1, between lines 13 and 14:

### BACKGROUND OF THE INVENTION

Please replace paragraph 2, page 2 with the following amended paragraph:

Consequently, there has been great interest in the question of the existence of periplasmic chaperones. However, unlike the well-characterized cytoplasmic machinery of *E. coli*, DnaK/DnaJ/GrpE and GroEL/GroES and possibly others (Makrides, 1996; Martin & Hartl, 1997; Buchner, 1996; EP 0 774 512 A3), the chaperone composition of the periplasm has remained poorly understood (Wall & Plückthun, 1995; Missiakas et al., 1996). While progress in elucidating the signal transduction of periplasmic stress has been made (Missiakas & Raina, 1997), the ultimate effector molecules controlling periplasmic folding have remained obscure, although some proteins, such as FkpA or SurA, were believed to act as general periplasmic folding catalysts (Missiakas et al., 1996). FkpA has first been described as very similar to the eukaryotic FK506 binding proteins (FKBPs) (Horne and Young, 1995), a class of well-characterized peptidyl-prolyl *cis-trans* isomerases (PIs), which have been shown to be inhibited by the macrolipide FK506. Missiakas and co-

workers showed, that the mature FkpA is located in the periplasm and assayed its activity (Missiakas et al., 1996). The estimated  $K_{cat}/K_m$  of the cis-trans isomerization of the Ala-Pro peptidyl-prolyl bond using succinyl-Ala-Ala-Pro-Phe-4-nitroanilide (SEQ ID NO:1) as substrate was  $90\text{mM}^{-1}\text{s}^{-1}$ . FkpA is directly regulated by  $\sigma^E$ , which binds in its promoter region (Danese and Silhavy, 1997). The  $\sigma^E$  pathway is induced by heat stress and conditions, that lead to misfolding or misassembly of outer membrane proteins (OMPs), such as over-expression of OMPs or inactivation of the surA gene.

Please add the following new paragraph at page 3, between lines 30 and 31:

#### **SUMMARY OF THE INVENTION**

Please replace paragraph 3 at page 13, line 17 with the following amended paragraph:

#### **~~FIGURE CAPTIONS~~ BRIEF DESCRIPTION OF THE DRAWINGS**